

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2005/012028

International filing date (day/month/year)
12.04.2005

Priority date (day/month/year)
15.04.2004

International Patent Classification (IPC) or both national classification and IPC
A61K31/495, A61P25/28, C07D295/18

Applicant
SAMARITAN PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b/s(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

01/27/06
D- RESP. DUE

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/012028

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/012028

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1-24,26; 25(part)

because:

- ☒ the said international application, or the said claims Nos. 1-24,26 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 25(part)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/012028

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-24,26,27
	No: Claims	25
Inventive step (IS)	Yes: Claims	1-24,26,27
	No: Claims	25
Industrial applicability (IA)	Yes: Claims	25
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III-1. Claim 25 is directed to composition comprising compounds (I) together with a pharmaceutically acceptable carrier. Many such compositions are known. The initial phase of the search revealed a thus very large number of documents relevant to the issue of novelty of claim 25. So many documents were retrieved that it is impossible to determine which parts of this claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search was performed taking into consideration the non-compliance in determining the extent of the search of claim 25. The search with regard to claim 25 is only complete for the example compound mentioned in the description. Some illustrative documents have been cited for the other parts of claim 25.

III-2. Claims 1-24 and 26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V-1. State of the Art:

The following documents have been cited:

- D1: WO 2004/108666 A (SAMARITAN PHARMACEUTICALS; GEORGETOWN UNIVERSITY; LECANU, LAURENT; GRE) 16 December 2004 (2004-12-16)
- D2: LECANU L ET AL: "Identification, design, synthesis, and pharmacological activity of (4-ethyl-piperazin-1-yl)-phenylmethanone derivatives with neuroprotective

- properties against beta-amyloid-induced toxicity" NEUROPHARMACOLOGY, PERGAMON PRESS, OXFORD, GB, vol. 49, no. 1, July 2005 (2005-07), pages 86-96, XP004963513 ISSN: 0028-3908
- D3: WO 2004/035556 A (GLAXO GROUP LIMITED; ANCLIFF, RACHAEL; ELDRED, COLIN, DAVID; FOGDEN, Y) 29 April 2004 (2004-04-29)
- D4: US-A-5 693 804 (DEBERNARDIS ET AL) 2 December 1997 (1997-12-02)
- D5: WO 01/07435 A (MERCK PATENT GMBH; BOETTCHER, HENNING; GREINER, HARTMUT; HARTING, JUER) 1 February 2001 (2001-02-01)
- D6: US 2004/034019 A1 (TOMLINSON RONALD ET AL) 19 February 2004 (2004-02-19)
- D7: DE 23 04 155 A1 (ICHTHYOL-GESELLSCHAFT CORDES, HERMANNI & CO, 2000 HAMBURG) 1 August 1974 (1974-08-01)
- D8: YUNG D K ET AL: "POTENTIAL ANTI ARRHYTHMIC AGENTS SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF SOME PIPERAZINE AND ETHYLENEDIAMINE ANALOGS OF PROCAINAMIDE 1 N PROPYL-4-BENZOYL PIPERAZINE HYDRO CHLORIDE 1 N BUTYL-4-BENZOYL PIPERAZINE HYDRO CHLORIDE 1 N PROPYL-4-P-METHOXYBENZOYL PIPERAZINE HYDRO CHLORIDE 1 N PROPYL-4-P" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 57, no. 12, 1968, pages 2073-2080, XP009055767 ISSN: 0022-3549
- D9: FUKUSHI H ET AL: "SYNTHESIS AND PLATELET-ACTIVATING FACTOR (PAF)-ANTAGONISTIC ACTIVITIES OF 1,4-DISUBSTITUTED PIPERAZINE DERIVATIVES" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN, TOKYO, JP, vol. 42, no. 3, March 1994 (1994-03), pages 541-550, XP001118308 ISSN: 0009-2363
- D10: YOUNES-EL-HAGE S ET AL: "SYNTHESE ET ETUDE DE L'ACTIVITE ANTIDEPRESSIVE D'ARYL ET HETEROARYL CARBOXAMIDES DE LA BENZYLPIPERAZINE SYNTHESIS AND ANTIDEPRESSIVE ACTIVITY STUDY OF ARYL AND HETEROARYL CARBOXAMIDES OF BENZYLPIPERAZINE" ANNALES PHARMACEUTIQUES FRANCAISES, MASSON, PARIS, FR, vol. 58, no. 4, 2000, pages 254-259, XP008031993 ISSN: 0003-4509
- D11: YOUNES S ET AL: "Synthesis and structure-activity relationships of novel arylalkyl 4-benzyl piperazine derivatives as sigma site selective ligands" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS

- SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 35, no. 1, January 2000 (2000-01), pages 107-121, XP004350211 ISSN: 0223-5234
- D12: BAZIARD-MOUYSSET G ET AL: "Synthesis and structure-activity relationships of novel 2-amino alkyl chromones and related derivatives as sigma site-selective ligands" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 33, no. 5, June 1998 (1998-06), pages 339-347, XP004127366 ISSN: 0223-5234
- D13: CARCELLER E ET AL: "(PYRIDYLCYANOMETHYL)PIPERAZINES AS ORALLY ACTIVE PAF ANTAGONISTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 35, no. 22, 1992, pages 4118-4134, XP002044180 ISSN: 0022-2623

D1-D3 are P-documents and will be disregarded in the PCT-procedure.

In the following paragraphs references to the above documents relate to the parts indicated in the search report unless specified otherwise.

V-2. Novelty (Art. 33(2) PCT):

Although no complete search could be carried out for claim 25 it is nevertheless clear that claim 25 does not define novel subject-matter since D7-D13 disclose compositions included in its scope.

Claims 1-24, 26 and 27 are novel over D7-D13 because D7-D13 do not mention the use of the disclosed compounds for treating Alzheimer or neuropathy.

Claims 1-24, 26 and 27 are novel over D4-D6 which deal with compounds useful in the treatment of Alzheimer's disease. The compounds of D4 and D6 differ in the substituent corresponding to CH₂-X in the present claims. The compounds of D5 have a benzimidazole instead of the phenyl ring.

V-3. Inventive step (Art. 33(3) PCT):

Closest state of the art can be seen in D4 which deals with compounds that differ in the substituent corresponding to CH₂-X in the present claims (i. a. by an additional carbonyl group). The problem to be solved would be to find other compounds which can be used to treat Alzheimer's disease. D7-D13 disclose unrelated uses. The compounds of D6 differ from the claims in the same substituent as D4 and D5 describes benzimidazoles. The skilled man would thus have no motivation to arrive at the present claims 1-24, 26 and 27 in order to find compounds useful for the claimed purposes.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO2004/108666	16.12.2004	20.05.2004	02.06.2003
WO2004/035556	29.04.2004	14.10.2003	16.10.2002